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ON EXTRACORPOREAL DIALYSIS OF BLOOD IN ACUTE ANURIA. THE IMPORTANCE OF β-OXIDATION IN THE KIDNEY TUBULES*

I. SNAPPER

THERE are many reasons why efforts to prolong the life of uremic and especially of anuric patients by extracorporeal dialysis of blood have attracted general attention. Autopsies of patients with anuria after burial under debris during the bombardment of London have shown that this condition was due to necrosis of the renal tubules—that is, of the epithelial part of the nephron, whereas the glomeruli were intact.[1] In general, necrosis of epithelial tissue is followed by complete regeneration. Thus, unless there is complete disruption of the renal structure,[2] acute anuria due to necrosis of the tubules is a reversible process. It has gradually transpired that many other instances of acute anuria—due to shock, incompatible blood transfusion, sulfa poisoning, hepato-renal syndrome, etc.—were also caused by damage to the tubules and not by obstruction of the tubules. The following explanation of the anuria seems a plausible one. As soon as the wall of the tubule dies, the tubular epithelium is transformed into a non-specific dialyzing membrane. Then the colloid

* From the Second Medical Service of the Mount Sinai Hospital, New York, N. Y. Presented December 18, 1951, before the Section on Medicine of The New York Academy of Medicine.

osmotic pressure of the blood plasma draws the water from the tubules towards the lumen of the tubular blood vessels and acute anuria results. In such cases, depressed renal blood flow must also be an important factor in the production of anuria.

In these cases the treatment must be aimed toward obtaining a survival period of more than twelve days after the beginning of the anuria. After a period of four days, regeneration of the tubules sets in and after about ten days urine secretion starts anew. As a matter of fact, the greater part of the patients who survived the anuric episode for more than ten or twelve days did recover.[3] Dialysis of blood which leads to the removal of many poisonous substances retained in the plasma must be one of the methods by which life can be prolonged.

Extracorporeal dialysis of blood of humans during life has for a long time been a dream of the experimental physiologists. Abel[4] in 1913 dialyzed blood of living animals. Haas, Necheles, Thalhimer and others improved Abel's technique until in 1943, Kolff[5] constructed an apparatus in which dialysis of blood of the living human patient could actually be performed. It is imperative to follow closely the change of the blood electrolytes occurring during dialysis. The introduction of the flame photometer which facilitates the rapid determination of the blood electrolytes has been a major factor in reducing the dangers of extracorporeal dialysis. The ideal goal of the experimentalists consists of restoration of the composition of the extracellular fluid of the anuric patient to normal. Here considerable caution is necessary.

During renal insufficiency, whether caused by glomerulonephritis or acute necrosis of the tubular apparatus, the sodium of the serum is low normal; chlorides, CO_2-combining power, and calcium are considerably decreased; urea, uric acid, creatinine, potassium, phosphates, and aromatic oxy-acids are increased. It seems at least doubtful whether it is advisable to try to increase the chlorides of the serum of uremic patients to normal values. Efforts to raise the chloride content of the serum during uremia have always had catastrophic results and thus attempts at restoration of homeostasis in uremia require great caution. At the same time it is highly questionable whether the increase of blood urea, uric acid and creatinine actually threatens life; the retention of these waste products is probably not of great clinical importance. The increase of the urea content of the serum may even have a diuretic effect. Thus the clinical efficacy of a method such as dialysis cannot be judged merely

by the large amounts of urea which are removed from the blood during the dialyzing period. This may well be unimportant as far as survival of the patient is concerned. It is certain that the accumulation of at least two dialyzable substances in the blood of the anuric patient—that is, of potassium and of inorganic and aromatic acids, threatens life. Since these substances are dialyzable, they can easily be removed by extracorporeal dialysis. For the time being, we should not be over ambitious. In most cases we should be satisfied to improve the condition of anuric patients by the removal of these two toxic substances and should not always strive for restoration of homeostasis of the plasma. In order to prevent heart failure, it may be necessary to remove part of the extracellular fluid during the dialysis. This requires very careful adjustment of the osmotic pressure of the dialyzing fluid and continuous checking of osmotic pressure and electrolyte content of the serum of the patient.

Since accumulation of potassium and acids is so important in determining the ultimate prognosis of acute anuria, it should be our aim to reduce the formation of these substances during the anuria as much as possible. During the oliguric and anuric phase the amount of fluid given to the patient should be restricted. Unless fluid is lost by vomiting or by diarrhea, the fluid intake should not exceed 800 cc. or maximally 1000 cc. and this fluid should not contain potassium. Fruit juice is high in potassium. Therefore no orange juice should be given to these patients, but this popular drink should be replaced by sugar water or weak tea with sugar. It is generally accepted that if only fluid and no calories are given during the anuria, protein of body cells will be used to provide calories. Destruction of cells will take place and potassium will be released. In order not to increase the hyperpotassemia inordinately, it seems advisable to administer calories during the anuric stage. The calory-providing food should be chosen in such a way that no substances are formed which would burden the function of the damaged kidney.

Borst[6] has advised feeding the anuric patient with butter and sugar. For this purpose 200 grams of ground sugar are suspended in 200 grams of melted butter and about 12 grams of flour and coffee flavor are added. This mixture is put into the icebox and is then divided into small butter-sugar balls. It has been difficult in practice to persuade patients to swallow these unsavory butter balls. More popular is the treatment advocated by Bull.[7] A mixture of 400 grams of glucose and 100 grams of peanut oil is emulsified with acacia gum and diluted with water to 1 liter. This

emulsion is given daily by continuous intragastric drip via a plastic intranasal tube 2-3 millimeters in diameter. Not every patient tolerates this mixture. It also has caused vomiting and diarrhea.

It is advisable to remove potassium from the plasma in the course of the anuria, even before a considerable degree of hyperpotassemia has been reached and before changes in the electrocardiogram can be discovered. Potassium can be removed by lavage of the small intestine.[8] Kelley and his associates[9] have placed a Levine tube in the stomach and a Miller-Abbott tube in the jejunum. In the course of twenty-four hours 4 liters of a solution containing 0.6 per cent Na Cl, 0.3 per cent $NaHCO_3$, 0.01 per cent calcium gluconate and 2 per cent of glucose are introduced via the Levine tube and sucked out via the Miller-Abbott tube. By this lavage large amounts of potassium can be removed within a few hours. This method is so effective that every few hours the potassium content of the serum must be determined in order to prevent dangerous hypopotassemia. The acidosis which develops during anuria can be combated by intravenous injections of 5 per cent sodium bicarbonate. Here caution is necessary because of the danger of pulmonary edema. Since anemia interferes with the function of the kidney, transfusions of packed cells are helpful. The amounts of sodium citrate introduced with the red cells may have a beneficial effect upon the acidosis. It must be added that the handling of patients who develop anuria after an operation is much more complicated. It is difficult to estimate exactly how much extra fluid and salts the postoperative condition of these patients requires. Comparable difficulties are encountered when the anuric patient develops fever.

Careful conservative treatment of acute anuria will often keep the patients in good condition for more than ten days. Usually spontaneous urinary secretion sets in before extracorporeal dialysis becomes necessary and it is generally estimated that about 85 per cent of the cases with acute anuria clear up with conservative treatment. Only exceptionally tenacious cases of anuria will require extracorporeal dialysis. The same holds true for patients whose treatment during the initial period of anuria has been unsatisfactory.

The beneficial effect of extracorporeal dialysis consists only of the removal of small molecular substances from the blood. It is at best an artificial apparatus substituting for the ultrafiltration which takes place at the level of the glomeruli and for the transportation of these substances through the tubular lumen. The function of the kidney, how-

ever, is much more complicated. Not only do the tubular cells actively secrete large molecules from the blood to the tubular lumen, they also reabsorb colloid substances like proteins, cholesterol, etc. In addition, non-excretory functions such as synthesis and specific oxidations are carried out in kidney cells. The following paragraphs will serve to underline the difference between the actual functions of the kidney and the extracorporeal dialysis.

1. Recently it has been emphasized that complex enzymatic systems located in the cells of the tubules play an important role in the function of the kidney.[10] In order to reabsorb substances from the lumen of the tubule against a gradient into the blood, energy is necessary. The same holds true for the transport of large molecules from the blood to the tubular lumen. The energy required for tubular reabsorption and secretion is obtained by the same enzymatic processes which render muscular contraction and propagation of nerve impulses possible,—that is, by the utilization of the energy present in certain phosphate bonds. For this purpose adenylic acid and inorganic phosphates are conjugated in the tubular cells by aerobic phosphorylation until adenosine triphosphate results. The potential energy present in the phosphate bonds of the latter substance is liberated by phosphatase activity and used for the reabsorption, secretion and synthesis performed by the tubular cells. When aerobic phosphorylation is inhibited by administration of certain substances, such as dinitrophenol, the transportation of phenolred, diodrast, and also of para-aminohippuric acid from the blood to the tubular lumen is inhibited. In this way the metabolic functions of the tubular cells have been closely linked to the excretory and secretory functions of the nephrons.

These modern conceptions have revived the interest in metabolic, non-excretory functions of the kidney. Whereas the production of energy by the enzymatic processes occurring in renal cells follows the common pattern of phosphorylation as present in the cells of many different organs, the kidney is also capable of performing more specific syntheses and oxidations.

2. It is superfluous to stress the importance of the formation of ammonia in the kidney. Classical experiments have proved that the ammonia excreted in the urine is produced in the kidney tubule by degradation of glutamine under influence of glutaminase to glutamic acid and ammonia. The latter substance is also formed by the action of an

α-amino-oxydase on certain amino acids.[11] When acidosis sets in, the amount of ammonia produced increases rapidly. Since the ammonia formation permits neutralization and excretion of acid without loss of large amounts of fixed base, ammonia production by the kidney is one of the principal mechanisms by which the deleterious influence of acidosis is minimized.

3. The kidney can synthesize hippuric acid from benzoic acid and glycin. It also synthesizes phenaceturic acid from phenylacetic acid and glycin.

The synthesis of hippuric acid takes place in the intact kidney if the organ is perfused with blood, containing sodium benzoate. During perfusion of the intact kidney with plasma or saline and sodium benzoate, this synthesis does not occur. The same holds true when suspensions of renal cells are used. Thus there are certain functions of the intact kidney that cannot be accomplished by suspensions of kidney cells.

4. By perfusion of the isolated kidney with blood containing aromatic fatty acids, it can be shown that the kidney performs the following oxidation's.[10] Phenylpropionic acid ($C_6H_5CH_2\ CH_2\ COOH$) to benzoic acid (C_6H_5COOH). Phenylbutyric acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ COOH$) to phenylacetic acid ($C_6H_5\ CH_2\ COOH$). Phenylvalerianic acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ CH_2\ COOH$) to benzoic acid. Phenylcapronic acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ CH_2\ CH_2\ COOH$) to phenylacetic acid.

The latter two oxidations consist of two consecutive β-oxidations.

In the liver an incomplete β-oxidation of fatty acids and of amino acids to diacetic acid, and β-hydroxybutyric acid takes place. The liver, however, does not oxidize either of these substances. The kidneys —and incidentally, also the muscles—complete this partial β-oxidation and during perfusion of the intact kidney large amounts of both these so-called ketone bodies disappear.[12]

It is interesting that acetate which must be liberated during the oxidations of aromatic fatty acids and of ketone bodies strongly increases the excretion of para-amino hippuric acid by the tubules. In this way β-oxidation by the kidney tubules does not only act as a detoxifying mechanism, but at the same time it favors the excretion of large molecules by these tubules.

It should be stressed that β-oxidations in kidneys of different species are not always the same. Whereas the isolated intact human kidney

easily oxidizes phenylpropionic acid to benzoic acid and excretes it in the urine as hippuric acid, the isolated kidney of the dog performs only a partial oxidation of phenylpropionic acid. During perfusion of the dog's kidney two H atoms are removed from the two CH_2 groups of the phenylpropionic acid, resulting in the formation of cinnamic acid (C_6H_5 CH = CH COOH). The latter substance then appears in the urine, excreted by the perfused kidney, in the form of cinnamoylglycin, but no hippuric acid is formed.[13]

It follows that when the kidney is diseased, or when the tubular apparatus is temporarily out of function, a syndrome must result which is due to—

the abolition of excretion of small molecular substances which under normal circumstances leave the kidney via glomeruli and are transported by the tubules;

the abolition of secretory processes and absorption of colloids by the tubules;

the abolition of synthesis and oxidation by the tubules. The absence of the latter processes may leave large amounts of toxic substances in the organism which under normal circumstances would have disappeared or been detoxified.

Extracorporeal dialysis at best replaces the excretion of small molecular substances which under normal circumstances are excreted by the glomeruli. It cannot replace either the tubular secretion or the synthesis and oxidations which under normal circumstances are performed by the kidney. The clinical syndrome of uremia does not depend only upon retention of substances which should have been excreted by the glomeruli and transported by the tubules. The dangers for life inherent in the absence of tubular secretion and of synthesis and oxidation by the kidney parenchyma should not be underestimated.

We know that retention of potassium and acids caused by the absence of the transport function of the kidney tubules threatens life. It is therefore a major advance that by the introduction of extracorporeal dialysis the dangers inherent in potassium and acid retention can be lessened. The detoxifying functions of the kidney which result from synthesis and oxidation and also from the function of tubular secretion are not replaced by extracorporeal dialysis. It thus seems advisable to avoid the designation "artificial kidney" for the apparatus in which the blood is dialyzed. Even if the dangers of hyperpotassemia and acidosis

have been overcome by dialysis, life may still be endangered by the abolition of the secretion of large molecules by the tubules and also by the products of insufficient renal synthesis and oxidation. This may well be the reason why exchange transfusion has proved to be helpful in the treatment of certain cases of acute anuria, although the quantities of small molecular substances removed by this method are negligible compared with the results of extracorporeal dialysis.[14]

SUMMARY

Extracorporeal dialysis permits removal of small molecular substances from the blood. Use of the artificial kidney can improve the condition of patients with anuria by removal of potassium and acids. It is true that many other substances are also removed by extracorporeal dialysis, but, as far as is known, the other dialyzable compounds, retained in the blood during anuria, do not endanger life. Treatment of the anuric patient should consist of fluid restriction, possibly feeding with moderate amounts of sugar and fat, combating of acidosis by intravenous sodium bicarbonate injections and of hyperpotassemia by intestinal lavage. In the correctly treated patient with acute anuria, extracorporeal dialysis will only rarely be necessary.

It is emphasized that use of the artificial kidney at best only replaces the glomerular filtration but not the secretion of larger molecules by the tubules nor the conjugation and oxidation in the tubules. The importance of β-oxidation taking place in the tubular cells is emphasized. Since lack of detoxification and oxidation of toxic substances during anuria continues, successful removal of dialyzable toxic products by the use of the artificial kidney may not be sufficient to save the life of the uremic patient.

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